62. (New) The composition of claim 34, wherein the biotin is selected from the group consisting of L-biotin, D-biotin and derivative thereof.

63. (New) The composition of claim 34, wherein the chemokine is selected from the group consisting of the chemokines of Table 1.

64. (New) The composition of claim 34, wherein the chemokine has a carboxyl terminus and the biotin is covalent attached to the carboxyl terminus of the chemokine.

65. (New) The composition of claim 34, wherein the biotin is covalently coupled to the pharmacologically active chemokine via a linker molecule.

Remarks

In the previous Office Action response, Applicants cancelled claims 6, 7, 27 and 56-58.

New claims 59-65 are added. Support for these claims can be found in previously pending claims 10, 11, 41 and 44-47. Claims 1, 10, 11, 15, 20-24, 34, 41-55 and 59-65 are currently pending.

No new matter has been added.

Claim Fees

There are currently thirty-two total claims and two independent claims pending.

In the Response to the Notice to File Missing Parts, Applicants paid for twenty-one total claims (i.e., paid for one additional total claim), and seven independent claims (i.e., paid for four additional independent claims). Applicants later re-introduced cancelled claims following the Response to Restriction Requirement. Prior to this and the previous amendments, there were thirty-one total claims and two independent claims pending. It is unclear whether, at that time, the Examiner charged the Deposit Account of the undersigned for the additional ten total claims.

If the Deposit Account was charged, then the Examiner is hereby requested to charge the Deposit Account for one additional total claim (large entity). If the Deposit Account was not charged previously for any of the re-introduced claims, then the Examiner is hereby requested to charge the Deposit Account for eleven additional total claims (large entity).

The Claimed Invention

The claimed invention provides compositions of biotin conjugates comprised of biotin covalently coupled to a pharmacologically active chemokine. The biotin conjugate is provided in a complex with an anti-biotin antibody that is selectively bound to biotin (claim 1, and claims dependent thereon). Alternatively, the biotin conjugate is provided together with a pharmaceutically acceptable carrier suitable for parenteral administration (claim 34).

The chemokines can be agonists or antagonists. The anti-biotin antibodies can comprise a therapeutic agent or a diagnostic agent. The anti-biotin antibody can also be a dual specificity antibody in which case it binds to biotin as well as another antigen such as a tumor cell associated antigen or a viral associated antigen. Anti-biotin antibodies can be those having an affinity constant ranging from about 1 to 100 nM. The complex of biotinylated chemokine and anti-biotin antibody can have a half-life of one day to one month or one week to two weeks, or alternatively about 15 minutes to about 1 hour in the presence of supra physiological levels of biotin.

The compositions of the invention have several in vitro and in vivo uses as discussed in the specification and herein.

Rejection Under 35 U.S.C. §112, first paragraph

The Examiner has maintained the rejection of claims 10, 11, 15, 20, 22-24, 34 and 41-55 under 35 U.S.C. §112, first paragraph because "the specification, while being enabling for a complex comprising an anti-biotin antibody and biotinylated eosin and a complex comprising an anti-biotin antibody and biotinylated ITAC in an experimental protocol of lymphocyte recruitment to the peritoneum, does not reasonably provide enablement for complexes consisting of any other biotinylated conjugate."

In the prior Office Action, the Examiner rejected all pending claims on the same grounds as those stated above. However, the Examiner has now withdrawn that rejection with respect to claims 1 and 21. Applicants presume that the Examiner is now acknowledging that the specification is enabling for complexes of anti-biotin antibody with any biotinylated chemokine (i.e., the full scope of claim 1). Applicants are therefore confused as to the outstanding enablement rejection of claims depending from claim 1. If the specification is sufficient to enable claim 1 (which the Examiner states it is), then the specification should similarly be sufficient to enable claims of narrower scope (i.e., claims that depend from claim 1). This is particularly true since the basis of the Examiner's maintained rejection is that the specification

does not teach "any other biotinylated conjugate". If the Examiner now states that claim 1 is enabled for "any other biotinylated conjugate", then all dependent claims should similarly be enabled for that limitation. Accordingly, Applicants respectfully request that the Examiner reconsider and clarify this rejection.

Notwithstanding Applicants' belief that previously pending claims 10, 11, 15, 20, 22-24 and 41-55, and new claims 56-62 are enabled if claim 1 is enabled, particularly in view of the basis of the Examiner's rejection, Applicants respectfully traverse the rejection for the reasons as set forth below.

Applicants previously addressed the enablement rejection with a analysis of the Wands factors in order to establish that the claimed invention could be made and used without undue experimentation by one of ordinary skill in the art. Applicants reiterate the arguments of record. In addition, Applicants now address the statements presently made by the Examiner.

At the outset, Applicants respectfully point out that the claimed invention relates to compositions of biotinylated chemokines either in the presence of an anti-biotin antibody (claim 1), or a pharmaceutically acceptable carrier suitable for parenteral administration (claim 34). Claims relating to methods of using such compositions were restricted out of this application previously, and thus are not currently pending in this application. Accordingly, the specification must enable how to make and use the claimed compositions of biotinylated chemokines and complexes of such chemokines with anti-biotin antibodies.

How to Make:

In the previous Office Action response, Applicants described in detail the teachings in the specification as well as the knowledge in the art relating to the synthesis of the claimed compositions. Specifically, the specification together with the knowledge in the art at the time of filing allows one of ordinary skill to select suitable chemokines (pages 1, 4, 12, 13, 25, 26, 44 and 45), make chemokine derivatives that are agonists or antagonists (page 5, lines 8-18; page 14, lines 21-32; page 15, lines 1-6; page 17, lines 8-22), biotinylate such chemokines (or alternatively, purchase them from a commercial manufacturer) (page 13, lines 15-30-32; page 14, lines 1-21; pages 15-17; Example 1), make anti-biotin antibodies (or alternatively, purchase them from a commercial manufacturer) (page 17, lines 31-32; pages 18-23; Example 2), screen anti-biotin antibodies for their affinity to biotin (pages 18-20, 23, Example 2), select and conjugate suitable diagnostic or therapeutic agents to anti-biotin antibodies (pages 26-27), select

and make suitable dual specificity antibodies (pages 23-26), make complexes of biotinylated chemokines and anti-biotin antibodies (page 18-19; Example 4), test such complexes for their half-life in the absence or presence of supra-physiological concentrations of free biotin (pages 18-19), and make pharmaceutically acceptable carriers suitable for parenteral administration (page 33, lines 8-23). Using the methodology provided in the specification, Applicants have synthesized a number of other biotinylated chemokines of different classes including CC chemokines such as human MIP1α (CCR1 ligand and CCR5 ligand), murine eotaxin (CCR3 ligand), human and murine MDC (CCR4 ligand), murine TARC (CCR4 ligand), human and murine MIP-3α (CCR6 ligand), human I-309 (CCR8 ligand), human CCL27 (CCR10 ligand), human CCL28 (CCR10 ligand); CXC chemokines such as human ITAC (CXCR3 ligand); and CX3C chemokines such as human fractalkine (CX3CR1 ligand). As noted below, Applicants have also confirmed the biological activity of these latter biotinylated chemokines.

In view of these teachings and the knowledge in the art at the time of filing, undue experimentation is not required to make the compositions of the invention.

How to Use:

The Examiner apparently rejects the claims for lack of enablement of treatment of diseases in vivo. Respectfully, this is not the standard by which the pending claims should be examined because these claims do not recite a use limitation. MPEP § 2164.01(c) states that when a "composition claim is not limited by a recited use (as in the present case), any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for nonenablement based on how to use." Enablement rejections based on a particular use should only be made when a composition claim is limited to such use. In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991). Since the pending claims do not recite a particular use limitation, any use that correlates with the entire scope of the claim should preclude an enablement rejection.

The Examiner's rejection is based on a therapeutic use of the claimed compositions. For example, the Examiner states "the specification has not demonstrated the adequate delivery of the complex and the release of the active chemokine to remedy an actual disease state in an organ or the blood stream vs a model of experimental lymphocyte recruitment to the peritoneum." As noted above, this standard is incorrect because the claims are not limited to therapeutic uses. Furthermore, the specification discloses uses in addition to therapeutic uses.

For example, the specification teaches that the claimed compositions can be used for imaging cells, a process that does not require a therapeutic effect. (See page 26, lines 29-30.)

The specification also teaches other uses of the claimed compositions including but not limited to *in vitro* or *in vivo* chemokine delivery to cells (page 3, lines 5-7), modulation of immune responses (page 3, line 16), modulation of recruitment of migratory cells to site of inflammation (page 3, line 17), *in vitro* or *in vivo* targeted delivery of agents (diagnostic or therapeutic agents) to pre-selected cells (page 3, lines 20-21), partial or complete elimination of particular cells either *in vivo* or *in vitro* (page 30, lines 8-20), desensitization of particular cells prior to re-infusion into a subject (page 12-17), and identification of cell populations expressing particular chemokine receptors *in vivo* or *in vitro* (page 31, lines 5-15).

The specification provides working examples that support several of the afore-mentioned uses. For example, the specification demonstrates that (1) biotinylated chemokines bind specifically to their respective receptors with efficiencies similar to their unbiotinylated counterparts (a similar observation has also been made for biotinylated chemokines synthesized since the filing of this application, as mentioned earlier) (Example 3); (2) biotinylated chemokines induce the migration of chemokine receptor transfectants in an *in vitro* system that is predictive of results obtained in *in vivo* chemotaxis assays (Example 4); (3) biotinylated chemokines when complexed with anti-biotin antibodies inhibit leukocyte migration into the peritoneum in an *in vivo* animal model in a chemokine- and leukocyte-specific manner (Examples 4b, 4c, 4d); and (4) inhibition of leukocyte chemotaxis *in vitro* following exposure of leukocytes to chemokines in vivo (Example 4e).

These examples sufficiently support the disclosed uses of the claimed compositions. For example, the demonstration that the complexes of biotinylated chemokine and anti-biotin antibody inhibit migration of specific leukocyte classes to the peritoneum following immune challenge supports the use of such complexes *in vivo* in the modulation of immune responses involving leukocyte migration to sites of inflammation. As another example, the demonstration that biotinylated chemokines bind to their respective receptors with efficiency similar to their unbiotinylated counterparts and that administration of chemokines in vivo makes leukocytes refractory to later exposure to the same chemokines supports the use of biotinylated chemokines in desensitizing cells either *in vivo* or *in vitro*. Accordingly, the specification satisfies the enablement requirement under 35 U.S.C. § 112, first paragraph because it enables a use that reasonably correlates with the entire scope of the rejected claims.

With respect to the references appended to the previous Office Action response, the Examiner states that they were not considered persuasive because "the instant invention .. is not chemokines per se but pharmaceutical agents comprising an anti-biotin antibody complexed to biotinylated chemokines administered in vivo". Applicants respectfully re-iterate that the claimed invention relates to compositions of biotinylated chemokines, either complexed with anti-biotin antibodies or in a pharmaceutically acceptable carrier suitable for parenteral administration. The appended references were intended to establish that G-protein coupled receptors and their ligands (including chemokines and their receptors) have been implicated in various disease states, and thus are reasonable therapeutic targets or agents. The Examiner's characterization of the invention as not directed to chemokines is incorrect. While the chemokines in the present invention are present in a conjugate with a biotin molecule and, in some instances, a complex with an anti-biotin antibody, the chemokine retains biological activity and is the pharmacologically active portion of the conjugate or the complex of the claimed compositions.

Finally, the Examiner states that "there is no teaching in the specification to explain how an antibody designed to release biotin in vivo will persist as a complex long enough to deliver the biotinylated chemokine to the site of the tumor or viral antigen." The specification teaches a suitable half-life range for complexes of anti-biotin antibody and biotinylated chemokines (pages 17-20). Moreover, the specification teaches that antigen/antibody complexes are tested for their ability to dissociate in the presence of supra-physiological concentrations of biotin, i.e., the complexes dissociate in a controlled manner dependent upon the administration of exogenous biotin at levels above those normally present in a subject. The specification also teaches sustained release or delayed release delivery compositions to further extend the half-life of the complex (page 34, lines 11-32; and page 35, lines 1-4). The teachings of the specification enable one of skill in the art to select anti-biotin antibodies with suitable affinities for biotin, to make complexes comprising such antibodies, to measure the dissociation of such complexes in the presence or absence of varying concentrations of biotin, and to tailor the release and availability of the complex to the accessibility requirements of the specific disease state. Furthermore, it is within the skill of the ordinary artisan to determine the times required for administered complex and separately administered biotin to reach tumor or infection sites, and thus to calculate the optimum time between complex and biotin administration to a subject.

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw the enablement rejection of now pending claims 10, 11, 15, 20, 22-24, 34 and 41-55 under 35 U.S.C. 112, first paragraph. For these same reasons, new claims 59-65 are similarly enabled by the specification.

Rejection Under 35 U.S.C. §103(a)

The Examiner has rejected claims 1 and 21 under 35 U.S.C. §103(a) as being unpatentable over DeVico et al. (USP 6,214,540), in view of Mehta et al. (USP 6,303,325). According to the Examiner, "DeVico et al. teach a biotinylated chemokine and a method of labeling or detecting a biotinylated chemokine by means of an antibody complex in place of avidin FITC." The Examiner acknowledges that "DeVico et al. do not specifically teach the formation of complex of biotinylated chemokine and an anti-biotin antibody in place of the avidin FITC." The Examiner relies on Mehta et al., however, to teach "an anti-biotin antibody for the general detection of biotin." The Examiner concludes that it would have been *prima facie* obvious to one of ordinary skill to use the specific anti-biotin antibody for the formation of a complex with the biotinylated chemokine, and that one of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Mehta et al. on the utility of the anti-biotin antibody in the detection of conjugated biotin."

Applicants respectfully traverse the rejection for the reasons set forth below.

Initially, Applicants respectfully disagree with the Examiner's reading of DeVico et al. DeVico et al. teach, *inter alia*, compositions and methods for treating and preventing HIV infection, that include chemokine proteins. The reference teaches that HIV infections can be treated or prevented by administering an effective amount of a pharmaceutical composition containing chemokine derivatives or analogs that bind a plurality of chemokine receptors. (See column 9, lines 44-49.) The reference makes a single mention of biotinylated chemokines. (See column 24, lines 26-30.) The reference teaches

> "cells that express human CD4 and one of the HIV co-receptors (e.g., CC CKR-5, CxC CKR4, etc.) are treated with biotinylated chemokine, derivative, or analogue and cell surface binding to each cell type is detected with an avidin FITC conjugate. Alternatively, other methods for labeling or detecting binding of the chemokine, derivative or analogue, such as antibodies, may be used." (See column 24, lines 26-32).

Accordingly, the reference teaches that the chemokines and their derivatives or analogs can be biotinylated, and that the binding of such biotinylated compounds to CD4-expressing cells can be assessed using avidin FITC. The reference also teaches that unbiotinylated chemokines can be

detected using antibodies specific for such chemokines. It does not teach anti-biotin antibodies, and accordingly it cannot teach the use of such antibodies to detect biotinylated chemokines. Therefore, the reference does not teach or suggest detection of "a biotinylated chemokine by means of an antibody complex in place of avidin FITC", as suggested by the Examiner. There is no motivation to use anti-biotin antibodies for this purpose because the reference teaches two methods of detection as set forth above, namely, avidin FITC or antibodies to chemokines.

In addition, DeVico et al. do not teach each and every element of claims 1 and 21. DeVico et al. do not teach a complex of a biotinylated chemokine and an anti-biotin antibody because, as argued above, DeVico et al. do not teach anti-biotin antibodies. DeVico et al. also do not teach a pre-formed complex of antigen and antibody because, in the most pertinent example provided by DeVico et al., cells are first exposed to unbiotinylated chemokines, followed by exposure to chemokine-specific antibodies. There is no mention of combining a chemokine and an anti-chemokine antibody to form a complex that is then applied to cells. With respect to claim 21, DeVico et al. do not teach an anti-biotin antibody comprising a diagnostic agent because again DeVico et al. do not teach anti-biotin antibodies.

Mehta et al. teach *in vitro* methods for determining and measuring analyte presence in a sample. The method involves bringing together a sample containing an analyte, a first and second binding agent (both of which can be biotin molecules), and an activator that binds the first and second binding agents. The activator can be an anti-biotin antibody.

If the references were combined, this combination still would not result in the claimed invention because the Mehta et al. teachings do not cure the deficiencies of DeVico et al. Mehta et al. do not teach the use of anti-biotin antibodies to detect biotinylated factors such as biotinylated chemokines. The first and second binding agents taught by Mehta et al. can be biotin, but they are not biotinylated factors such as biotinylated chemokines. Mehta et al. also do not teach a pre-formed antigen/antibody complex. Rather, Mehta et al. teach addition, to a reaction vessel, of first and/or second binding agents (e.g., biotin), separate in time from addition of activator (e.g., anti-biotin antibody). Finally, Mehta et al. do not teach anti-biotin antibodies that comprise diagnostic agents. Accordingly, claims 1 and 21 are not rendered obvious in view of the combination of DeVico et al. and Mehta et al. because this combination fails to teach each and every limitation of the rejected claims. The Examiner has failed to meet her burden of establishing a *prima facie* case of obviousness in view of the art of record.

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 1 and 21 under 35 U.S.C. §103(a) as being unpatentable over DeVico et al. (USP 6,214,540), in view of Mehta et al. (USP 6,303,325). New claims 59-65 which depend from independent and non-rejected claim 34 also are not obvious in view of these references.

Acknowledgement of Withdrawal of Rejections by Examiner

Applicants herewith acknowledge the Examiner's withdrawal of the rejection of claims 1 and 21 under 35 U.S.C § 112, first paragraph, enablement; claims 1, 6, 7, 10, 11, 15, 20-24, 34 and 41-55 under 35 U.S.C. § 112, first paragraph, written description; and claims 27 and 56-58 under 35 U.S.C. §102(e). Applicants thank the Examiner for her reconsideration and withdrawal of these previous rejections.

Summary

Applicants believe that each of the pending claims now is in condition for allowance. Applicants respectfully request that the Examiner telephone the undersigned in the event that the claims are not found to be in condition for allowance.

If the Examiner has any questions and believes that a telephone conference with Applicants' agent would prove helpful in expediting the prosecution of this application, the Examiner is urged to call the undersigned at (617) 720-3500 (extension 266).

Respectfully submitted,

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